Research Article

Fragmentation Pathways of Trifluoroacetyl Derivatives of Methamphetamine, Amphetamine, and Methylenedioxyphenylalkylamine Designer Drugs by Gas Chromatography/Mass Spectrometry

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Methamphetamine (MA), amphetamine (AM), and the methylenedioxyphenylalkylamine designer drugs, such as 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethylamphetamine (MDEA), *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB), 3,4-methylenedioxyamphetamine (MDA), and 3,4-(methylenedioxyphenyl)-2-butanamine (BDB), are widely abused as psychedelics. In this paper, these compounds were derivatized with trifluoroacetic (TFA) anhydride and analyzed by gas chromatography/mass spectrometry using electron ionization in positive mode. Gas chromatographic separation for TFA derivatives of all compounds was successfully resolved using an Equity-5 fused silica capillary column with a poly (5% diphenyl-95% dimethylsiloxane) stationary phase. Base peaks or prominent peaks of MA, AM, MDMA, MDEA, MBDB, MDA, and BDB appeared at m/z 154, 140, 154, 168, 168, 135, and 135, respectively. These occurred due to α -cleavage from the amide nitrogen, splitting into the TFA imine species and benzyl or methylenedioxybenzyl cations. Further prominent fragment ions at m/z 118 for MA and AM, m/z 162 for MDMA, MDEA, and MDA, and m/z 176 for MBDB and BDB were produced by cleavage of the phenylpropane or methylenedioxypropane hydrocarbon radical cation via a hydrogen rearrangement. These fragmentation pathways for the TFA derivatives of all the compounds are summarized and illustrated in this paper.

1. Introduction

In recent years, extensive attention in clinical and forensic toxicology has focused on the increasing abuse of methamphetamine (MA), amphetamine (AM), and methylenedioxyphenylalkylamine derivatives, such as 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxyethylamphetamine (MDEA), *N*-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB), 3,4-methylenedioxyamphetamine (MDA), and 3,4-(methylenedioxyphenyl)-2-butanamine

(BDB). A number of severe and even fatal intoxications attributable to these drugs have been reported [1–4]. Consequently, detection and identification analyses for these compounds are routinely performed in clinical and forensic laboratories.

Several gas chromatographic methods to analyze MA, AM, MDMA, MDEA, MBDB, MDA, and BDB in doping control and toxicological analysis have been reported [5–8]. Because of their relatively low molecular weights, high

FIGURE 1: Mass chromatograms obtained from GC/MS analysis using Equity-5 capillary column for TFA derivatives of seven analytes. The ionizing energy was 70 eV with an emission current of 60 μ A. Ten nanograms of each analyte were injected in the positive-ion EI mode. Peaks: (1) AM-TFA; (2) MA-TFA; (3) MDA-TFA; (4) BDB-TFA; (5) MDMA-TFA; (6) MDEA-TFA; and (7) MBDB-TFA.

polarity, and volatility, derivatization is necessary when using gas chromatography (GC) [9]. Acylation is one of the most popular derivatization reactions for primary and secondary amines and converts compounds into derivatives that are more easily separated or give an enhanced response in GC compared with the parent compound [10]. GC/mass spectrometry (MS) using the electron ionization (EI) mode is a widely used technique in drug analysis, as it leads to a number of fragment ions providing structural information [11]. Although quantitative analysis of MA, AM, and the methylenedioxyphenylalkylamine designer drugs has been frequently performed in clinical and forensic toxicology by GC/MS-EI with derivatization [8, 12–17], systematic studies of mass spectrometric behavior for these compounds have been limited [9, 18, 19]. In this paper, we present mass spectra and detailed fragmentation pathways for MA, AM,

MDMA, MDEA, MBDB, MDA, and BDB using GC/MS in EI mode after acylation derivatization.

2. Experimental Part

2.1. Materials. Hydrochloride salts of MDA, BDB, MDMA, and MBDB were prepared as described briefly here. MDA and BDB syntheses were performed according to the procedures described by Lindeke and Cho [20]. MDA was synthesized by hydrogenation of 1-(3,4-methylenedioxyphenyl)-2-nitropropene, which was prepared beforehand by condensation of piperonal and nitroethane. BDB was synthesized by hydrogenation of 1-(3,4-methylenephenyl)-2-nitrobutene, which was prepared beforehand by condensation of piperonal and nitropropane. MDMA and MBDB syntheses were performed according to the procedures described by

FIGURE 2: EI mass spectra of the TFA derivative of MA and their probable fragmentation pathway.

FIGURE 3: EI mass spectra of the TFA derivative of AM and their probable fragmentation pathway.

FIGURE 4: EI mass spectra of the TFA derivative of MDMA and their probable fragmentation pathway.

FIGURE 5: EI mass spectra of the TFA derivative of MDEA and their probable fragmentation pathway.

FIGURE 6: EI mass spectra of the TFA derivative of MBDB and their probable fragmentation pathway.

FIGURE 7: EI mass spectra of the TFA derivative of MDA and their probable fragmentation pathway.

Repke et al. [21]. MDMA and MBDB were prepared by hydrogenation of MDA and BDB, respectively, followed by benzyloxycarbonylation with benzyloxycarbonyl chloride. These four compounds, MDA, BDB, MDMA, and MBDB, were then finally converted to their hydrochloride salts.

MDEA hydrochloride was synthesized according to published procedures [22] that follow. Briefly, acetic anhydride was added to a solution of MDA free base in pyridine and the mixture was stirred at room temperature for 0.5 h. The reaction was quenched by addition of distilled water and

FIGURE 8: EI mass spectra of the TFA derivative of BDB and their probable fragmentation pathway.

acidified with hydrochloric acid. The aqueous mixture was extracted with diethyl ether and the organic phase was evaporated to dryness *in vacuo*. The residue, *N*-acetyl-3,4-methylenedioxyamphetamine, was recrystallized from ethyl acetate/hexane, and the crystalline product was added to

a solution of acetic anhydride and pyridine. The resulting solution of *N*-acetyl-3,4-methylenedioxyamphetamine was added to lithium aluminum hydride in anhydrous tetrahydrofuran and the reaction mixture was heated at reflux for three days. After cooling the reaction mixture on an ice-bath,

the excess hydride was decomposed by addition of distilled water then sodium hydroxide. The mixture was filtered and the solvent removed *in vacuo*. The residue was dissolved in ethyl alcohol and concentrated hydrochloric acid was added. This aqueous solution was extracted with ethanol/diethyl ether followed by diethyl ether, and the solvent removed *in vacuo*. Recrystallization of the residue gave MDEA hydrochloride.

AM sulfate was synthesized according to the literature procedure [20]. All the compounds described above were prepared at the Department of Forensic Medicine, Fukuoka University School of Medicine. The salts were pure and characterized by mass spectrometry. MA hydrochloride was purchased from Dainippon Pharmaceutical Co., Ltd. (Osaka, Japan). Trifluoroacetic (TFA) anhydride was obtained from Pierce (Rockford, Ill, USA). Other chemicals used were of the highest purity commercially available.

2.2. Preparation of Standard Solutions. Stock standard solutions of MA, AM, MDMA, MDEA, MBDB, MDA, and BDB were prepared separately by dissolving an accurately weighed amount of each compound in methanol to achieve a concentration of 1 mg mL⁻¹. All stock solutions were stored at 4°C. Working standard solutions from 1–5 µg 10 µL⁻¹ in methanol were prepared by serial dilution from the stock standard solutions. Ten microliter working standard solutions were evaporated to dryness under a gentle stream of nitrogen and the residue was used for derivatization.

2.3. Derivatization. MA, AM, MDMA, MDEA, MBDB, MDA, and BDB were derivatized with TFA anhydride. A 100 µL aliquot of TFA anhydride/ethyl acetate (5:1, v/v) was added to each residue, and samples were capped, mixed, and heated at 80°C for 10 min with an aluminum block heater (Reacti-Therm Heating/Stirring Model; Pierce). After cooling to room temperature, the solvent was then evaporated to dryness under a stream of nitrogen, and residues were reconstituted in 50 µL ethyl acetate. A 1 µL aliquot of sample solution was submitted for GC/MS analysis.

2.4. GC/MS Conditions. All analyses were performed using a Shimadzu GC-2010 gas chromatograph interfaced with a Shimadzu QP-2010 quadrupole mass spectrometer (Shimadzu Corp., Kyoto, Japan). The GC/MS was operated with an interface temperature of 300°C and an ionization source temperature of 250°C. The mass spectrometer was tuned daily, using perfluorotributylamine. A solvent delay of 4.0 min was set to protect the filament from oxidation. Chromatographic separation was achieved using an Equity-5 fused silica capillary column (30 m × 0.32 mm i.d., 0.25 µm film thickness, poly(5% diphenyl-95% dimethylsiloxane) stationary phase; Supelco, Bellefonte, Pa, USA). Helium, with a minimum purity of 99.99995%, was used as carrier gas at a constant pressure of 42.3 kPa (initial flow rate of 2 mL min⁻¹). The gas chromatograph was equipped with a split/splitless injection port, operated at 250°C. Samples were injected in the splitless mode, at a column temperature of 60°C, and the splitter was then opened after 1 min. The gas chromatograph oven temperature was programmed

as follows: initial temperature, 60°C for 1 min; from 60 to 200°C at 20°C min⁻¹; finally from 200 to 300°C at 40°C min⁻¹. The mass spectrometer was operated in the positive-ion EI mode using ionizing energy of 70 eV and emission current of 60 µA, or ionizing energy of 20 eV and emission current of 10 µA. Full-scan data were obtained with mass range of *m/z* 50–350, scan interval of 0.5 s, and scan speed of 769 amu/s.

3. Results and Discussion

TFA anhydride is the most widely used derivatizing agent, known to react with and acylate the primary and secondary amine groups of the amphetamine-type illicit drugs [8, 10, 12, 15–17, 23]. However, excess TFA and byproducts such as, trifluoroacetic acid, are produced in reactions with the target compounds [24]. These have to be removed from the extract prior to the GC/MS analysis, in order to avoid damaging to the GC column [25]. In the present study, our sample preparation of drying the reaction mixture with TFA anhydride under a stream of nitrogen and reconstituting the residue in ethyl acetate greatly reduced both excess derivatizing agent and the acid byproduct. The TFA derivatives of the seven compounds were well separated with good peak shapes and no remarkable impurities within 9.5 min (Figure 1). In the preliminary experiment, the mixtures of MA, AM, MDMA, MDEA, MBDB, MDA, and BDB were compared on different stationary phases using several temperature programs. The best compromise between analysis time and resolution was achieved on the Equity-5 capillary column.

Figures 2–8 show the EI full-scan mass spectra with ionizing energies of 70 eV and 20 eV for the TFA derivatives of MA, AM, MDMA, MDEA, MBDB, MDA, and BDB and their probable fragmentation pathways. The molecular ions for MA and AM were barely detectable and therefore of little quantitative value, at *m/z* 245 and *m/z* 231, respectively, (Figures 2 and 3). MDMA, MDEA, MBDB, MDA, and BDB produced molecular ions with relatively high abundance (6–12% at 70 eV and 9–53% at 20 eV) at *m/z* 289, 303, 303, 275, and 289, respectively (Figures 4–8). The relative abundance of molecular ions in the EI mass spectra of these derivatives may depend substantially on the chemical nature of substituents directly attached to the benzene ring, such as their inductive effect and/or their thermal stability.

MA and AM produced prominent peaks at *m/z* 154 and 140, respectively, in the mass spectra (Figures 2 and 3). These ions were the TFA imine species, probably by α -cleavage of the amide nitrogen of their parent molecules. This cleavage could also simultaneously lead to benzyl cation ([C₇H₇]⁺) fragment at *m/z* 91. The mass spectra for both derivatives showed high relative abundance ions at *m/z* 118 (35–44% for MA and 97–100% for AM), corresponding to the phenyl-propane hydrocarbon radical cation (Figures 2 and 3). The formation of this cation can be explained by a hydrogen rearrangement [26]. This involves migration of a γ -hydrogen atom from the alkyl group to the carbonyl oxygen through a cyclic six-membered transition state, followed by cleavage of the alkyl carbon-nitrogen bond in the side chain leading to the loss of imine species.

For MDMA, MDEA, and MBDB, prominent peaks at m/z 154 (for MDMA) and 168 (for MDEA and MBDB) and the 3,4-methylenedioxybenzyl cation peak at m/z 135 probably resulted from α -cleavage of the amide nitrogen (Figures 4–6). MDA and BDB both have H as a substituent on the nitrogen atom and both gave base peak ions at m/z 135 corresponding to the 3,4-methylenedioxybenzyl cation (Figures 7 and 8), produced via α -cleavage of the amide of their parent molecules. The spectra of these methylenedioxy derivatives showed characteristic fragment ions at m/z 162 for MDMA, MDEA, and MDA and m/z 176 for MBDB and BDB, with high relative abundance of 33–97% at 70 eV and 94–100% at 20 eV. Both of these fragment ions can be assigned as the methylenedioxyphenylpropane radical cation due to a hydrogen rearrangement (Figures 4–8).

The compounds with a methyl substituent on the nitrogen atom, MA, MDMA, and MBDB, gave a characteristic cation ($[\text{CH}_3\text{-N}\equiv\text{C-CF}_3]^+$) at m/z 110 (Figures 2, 4, and 6). MDEA with an ethyl substituent on the nitrogen atom produced analogous cation at m/z 124 corresponding to ($[\text{C}_2\text{H}_5\text{-N}\equiv\text{C-CF}_3]^+$), with low relative abundance of 4% at 20 eV and 7% at 70 eV (Figure 5). We propose that this resulted from the decomposition reaction of the four-membered nitrogen-containing heterocyclic intermediates in the fragmentation process of the m/z 154 or 168 cations (Figures 2, 4–6). In addition, the spectrum of MDEA showed a characteristic cation at m/z 140 with a relative abundance of 55% at 70 eV and 21% at 20 eV (Figure 5). This iminium ion probably originated from a rearrangement of the ethyl group of the m/z 168 cation to lose ethylene (C_2H_4). These results were consistent with the previous report [27].

Benzyl or tropylium cation at m/z 91 produced in MA and AM occurred due to a neutral loss of acetylene (C_2H_2), which gave rise to the cyclopentadienyl ion ($[\text{C}_5\text{H}_5]^+$) at m/z 65 (Figures 2 and 3). Thus, m/z 91/65 for MA and AM was typical fragment pairs of monosubstituted alkyl aromatics, although these ions are less favored in the mass spectra. The spectra for MDA and BDB showed complementary ions at m/z 140 and m/z 154, respectively, with relative abundance of 7% at 70 eV and 9–11% at 20 eV, corresponding to the TFA imine species. The ion of m/z 69 ($[\text{CF}_3]^+$) with 4–14% relative abundance at 70 eV was present in the TFA derivatives of all compounds.

4. Conclusions

The GC/MS-EI ionization mass spectra of TFA derivatives of MA, AM, and the methylenedioxyphenylalkylamines, MDMA, MDEA, MBDB, MDA, and BDB, were studied in positive mode. The main fragmentation pathways for all seven derivatives involved α -cleavage and a hydrogen rearrangement. Both pathways gave characteristic ions, occurring at m/z 154, 118, and 91 for MA; m/z 140, 118, and 91 for AM; m/z 162, 154, and 135 for MDMA; m/z 168, 162, 140, and 135 for MDEA; m/z 176, 168, and 135 for MBDB; m/z 162, 140, and 135 for MDA; and m/z 176, 154, and 135 for BDB. Additionally, MA, MDMA, and MBDB with a methyl substituent on the nitrogen atom had an intense ion at m/z 110 from the fragmentation process of the m/z

154 or m/z 168 prominent peak ions. These characteristic fragmentation patterns of TFA derivatives of MA, AM, and the methylenedioxyphenylalkylamine designer drugs will aid in the identification of these drugs from biological samples in clinical and forensic toxicology.

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